Fang Liu

A Mechanism for Cancer Cells to be Refractory to the to the Growth-Inhibitory Effects of TGF-*B*

[The goal of this project is to determine whether cyclin-dependent kinase (CDK) inactivates Smad3, which is expected to shed new insights into the mechanisms of cancer formation.]

Excessive cell proliferation is the hallmark of cancer. Cell proliferation is controlled by a family of proteins (enzymes) that are called cyclin-dependent kinases (CDKs). In order for cells to multiply, CDKs add phosphate groups to the tumor suppressor retinoblastoma protein (Rb). This modification inactivates Rb, thus allows cells to amplify. In the CDK family, CDK4 and CDK2 are the two critical CDKs fro cell proliferation. Thus far, Rb family members, which include Rb and its two cousins, are the only known targets of CDK4 and CDK2. Our recent studies have discovered that Smad3 negatively regulates cell proliferation and whether CDK inactivation of Smad3 can facilitate cell proliferation.

What do we know about Smad3? Smad3 plays a key role in mediating transforming growth factor-beta (TGF-*B*) growth-inhibitory effects. TGF-*B* is a protein that is the most potent physiological inhibitor of cell proliferation of many different cell types. Furthermore, TGF-*B* is the major inhibitor of human cancer formation at early stages. Two of the most potent chemopreventive drugs, retinoic acid (accutane) and tamoxifen, may exert their function by increasing the production of TGF-*B*, which then inhibits cell multiplication. The importance of TGF-*B* is the control of cancer incidence is underscored by the finding that over 90% of human malignant cancers have lost TGF-*B* mediated growth inhibition. The mechanism by which cancer cells are resistant to the growth-inhibitory effects of TGF-*B*, however, is not clear. Based on the observations that the activities of CDKs are very high in cancer cells and Smad3 is a very good target for CDK, we propose that CDK inactivation of Smad3 is a major mechanism for cancer cells to be resistant to TGF-*B*. We will initiate to examine this hypothesis in this proposal. We anticipate that the findings of this application will shed new insights for better understanding, preventing, and treating cancer.